PATENT COOPERATION TREATY

Rec'd PCT/PTO 20 JAN 2005

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

AMY H. Fix
GLAXOSMITHKLINE
Five Moore Drive, P.O. Box 13398
Research Triangle Park
North Carolina 27709
ETATS-UNIS D'AMERIQUE

NOV 0 4 2004

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	25.10.2004
Applicant's or agent's file reference: PU4757 WO	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 03/22719	21.07.2003	23.07.2002

Applicant
SMITHKLINE BEECHAM CORPORATION et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Hebert, W Tel. +49 89 2399-2152

Form PCT/IPEA/416 (January 2004)

EV332065417US

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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ...	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US 03/22719	International filing date *(day/month/year)* 21.07.2003	Priority date *(day/month/year)* 23.07.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/505		
Applicant SMITHKLINE BEECHAM CORPORATION et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
04.02.2004	25.10.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Fritz, M Telephone No. +49 89 2399-2792

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US 03/22719

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-64 as originally filed

Claims, Numbers

1-40 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 13-15,18-19,21-35

   because:

   ☒ the said international application, or the said claims Nos. 13-15,18-19 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 21-35

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 1-20,36-40 .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-9,12,17,20,38-40
	No:	Claims	1,10,11,16,36-37
Inventive step (IS)	Yes:	Claims	2-9,12,17,20,38-40
	No:	Claims	1,10,11,16,36-37
Industrial applicability (IA)	Yes:	Claims	1-12,16-17,20,36-40
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 13-15 and 18-19 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(i) PCT).

The examination is carried out only on the subject-matter searched, i.e. claims 1-12, 16-17,20 and 36-40.

Re Item IV:

Lack of unity of invention

This International Searching Authority found multiple inventions in this international application, as follows:

1. Claims: 1-20,36-40

Compounds of formula (I), pharmaceutical compositions thereof, methods of treatment involving the compounds (I), the use thereof in the preparation of a medicament and compounds of formula (V)

2. Claims: 21-25

Compounds of formula (II)

3. Claims: 26-30

Compounds of formula (III)

4. Claims: 31-35

Compounds of formula (IV)

Unity of invention requests a common technical feature which is a contribution to the art.
The claims of the present case refer to compounds of the general formula (I) and intermediates thereof of formulas (II), (III), (IV) and (V).
In a case of this kind (i.e. when final products and several intermediates are claimed) unity exists, if all of the compounds claimed comprise the same structural feature which serves to distinguish the final products from those of the prior art; moreover in the process for the preparation of the final products the intermediates should not be separated from each other and/or the final products by other intermediates which are already known in the art, i.e. in a process schematically represented as

Intermediate1 --> Intermediate2 --> Intermediate3 --> product

all of the compounds involved (Intermediate1, Intermediate2, Intermediate3 and product) must

a. share the same structural feature that distinguishes the product from the prior art

and

b. be novel

It is noted that it is evident from the description (p. 9ff) that the terms "alkyl" and "heteroaryl" have to be understood as comprising also the optionally substituted moieties.

Therefore none of the above conditions a. and b. is fulfilled in the present case, as the first document cited in the International Search Report cites both a compound which is a representative of the compounds (I) (compound 14) and a compound which is a representative of the compounds (V) (compound 6).

Furthermore the initial phase of the search revealed that a large number of representatives of the intermediates (III), (IV), and (V) are also known in the art. The present application comprises - by consequence - five different inventions.

In order not to put an undue burden on the applicant by demanding an excessive number of search fees, the claims referring to the compounds (I) and the intermediates (V)

were treated as one invention only.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: BHAT ET AL.: 'Pyrazolopyrimidine Nucleosides. 12. Synthesis and Biological Activity of Certain Pyrazolo[3,4-d]pyrimidine Nucleosides Related to Adenosine' J. MED. CHEM., vol. 24, 1981, pages 1165-1172, XP002267111

D2: WO 01/019829 A (BASF AG ;HIRST GAVIN C (US); RAFFERTY PAUL (US); RITTER KURT (US);) 22 March 2001 (2001-03-22).

For the assessment of the present claims 13-15, 18-19 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The following comments with regard to novelty and inventive step of claims only refer to the subject-matter concerning the first identified invention, i.e. claims 1-12,16-17, 20 and 36-40 (cf. International Search Report, sheet B).

It is stated in the description that "alkyl" and "heteroaryl" may also be substituted. When applying this extended definiton on the compounds (I) and (V) of the present case, the compounds 6 and 14 of D1 become representatives of the compounds (I) and (V), and the subject-matter of claims 1, 10, 11, 16 and 36-37 lacks novelty (Art. 33(2) PCT).

D1 is silent with regard to an eventual protein kinase inhibiting activity of the substances described therein.

D2 refers to pyrazolopyrimidine derivatives displaying kinase inhibiting activities, however none of these known compounds has a hydrazino-substituent in position 4.

The subject-matter of claims 2-9, 12, 17, 20 and 38-40 according to the present case is novel in the sense of Article 33(2) PCT.

Closest prior art is D2.

The problem of the present application was to provide further compounds that are useful as protein kinase inhibitors.

This problem has been solved by representatives of the compounds (I), as was shown in the description.

The group R^1-CH=N-N- attached to the 4-position of the pyrazolopyrimidine skeleton in the compounds (I) of the present case is a rather complex substituent which is neither disclosed nor suggested in D2. Those representatives of the compounds (I) which are a solution to the problem underlying the invention can thus not be considered obvious for the skilled man.

An inventive step in the sense of Article 33(3) PCT can therefore be acknowledged for the subject-matter of claims 2-9,12,17, 20 and 38-40.

Furthermore the following objections are raised:

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D2 is not mentioned in the description, nor are these documents identified therein.

The first structural formula in claim 1 is not complete, as the hydrogen at the nitrogen atom attached in 4-position of the pyrazolopyrimidine skeleton is missing.

The chemical nomenclature employed in the claims should - for clarity reasons - be kept unitary in order to avoid any misunderstandings. This could be done by substituting the term "pyridinyl" used in claims 2 and 3 by "pyridyl" (Art. 6 PCT).

Claim 20 contains a reference to the description. According to Rule 6.2 (a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here (see the Guidelines, C-III, 4.10).

The dependencies of claims 37-40 are not correct (Art. 6 PCT).

The vague and imprecise expression "spirit" employed in the description on page 64 implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them (see also the PCT Guidelines, III-4.3a).

Claims and description are not in accordance with each other, as requested by Article 6 PCT, since the scope of the groups "alkyl", "alkylene", "aryl", "heteroaryl" as defined in the description is broader than the skilled reader would expect it to be when reading the same terms in the claims (this reader would understand all these groups as being un-substituted).

It is - in this respect - noted that a term as "optionally substituted" which is not followed by a list of these possible substituents will be, when introduced into a claim, understood as non-limiting and - in an eventual European Phase of Examination - lead to an objection of this claim under Articles 83, 84 and 56 EPC (corresponding to Articles 5, 6 and 33(3) PCT).

The term "acyl" used in claim 1 is not precise enough (cf. definition on p. 10) giving rise to an objection under Article 6 PCT.

The same objection applies for the expression "pharmaceutically acceptable derivatives thereof" (claim 1) and "pharmaceutically functional derivatives thereof" (claim 36).